Remarks/Arguments

Following entry of the amendments to the claims presented herein, claims 26-29 and 36-72 are pending. The amendments to the claims and added claims 43-72 find support throughout the specification including from page 12, line 14 to page 40, line 8 of the present application.

Applicants acknowledge the Examiner's indication that the inventorship of this application has been amended to add Johan Selmer, Jeppe Sturis and Philip Just Larsen as inventors.

In response to the Examiner's objection to the specification on the basis that the specification fails to recite the appropriate sequence identifiers at each place where a sequence was discussed (citing to page 12, lines 21-31), Applicants note that on page 1 of the Preliminary Amendment filed on March 7, 2001, the application was amended to insert "(SEQ ID NO:1)" at page 12, line 31 and at page 22, line 11. Accordingly, withdrawal of this objection is therefore respectfully requested.

REJECTION OF THE CLAIMS UNDER 35 USC 102(a)

The Examiner rejected claims 26, 27, 36, 37 and 40 as anticipated under section 102 (a) by Bachovchin (WO 99/38501) in view of Howard [Current Opinion in Lipidology, (1994) 5:216-220].

Applicants respectfully traverse this rejection.

Bachovchin is cited as teaching "improved methods for reducing hyperlipidemia and/or hyperlipoproteinemia and for abating atherosclerosis (page 3, lines 19-21) and methods for producing beneficial changes in blood lipoprotein levels, and thus to provide effective treatments for diabetes, obesity and/or atherosclerosis (page 4, full paragraph 3)". The Examiner alleges that Bachovchin further teaches that an inhibitor which inhibits the proteolysis of GLP-1, and accordingly increases the plasma half life of GLP-1 (page 5, last full paragraph of Bachovchin), can be used in the aforementioned methods and that this inhibitor constitutes a "GLP-1 agonist". Howard is cited as teaching that the leading cause of death for individuals with diabetes is cardiovascular disease and that one of the most important factors that contribute to this is the alteration in lipoproteins that occur in diabetic subjects. (page 216, left column).

In reply, Applicants submit that the inhibitor taught by Bachovchin is not a "GLP-1 agonist" as set forth in the present claims. In particular, Bachovchin teaches the use of peptide and non-peptide inhibitors of dipeptidylpeptidase IV (DPPIV), the enzyme that degrades GLP-1 (see, for example, page 3, lines 27-29 and page 33, line 13 to page line 27 of Bachovchin).

By comparison, independent claims 26, 37 and 40 have been amended to recite that the GLP-1 agonist is GLP-1 (7-37), GLP-1 (7-36) amide, exendin-3 or exendin-4 or an analogue or derivative of any of the foregoing.

Accordingly, as the inhibitor of Bachovchin is not GLP-1 or an analogue or a derivative thereof, or exendin or an analogue or a derivative thereof, Bachovchin and Howard do not teach the use of a "GLP-1 agonist" as defined in the present application and cannot be held to anticipate claims 26, 27, 36, 37 and 40. Withdrawal of this rejection is therefore respectfully requested.

REJECTION OF THE CLAIMS UNDER 35 USC 102 (b)

The Examiner rejected claims 26-29 and 36-42 as anticipated by Eng (US patent 5,424,286) in view of Raufman et al [J.Biol. Chem., (1992) 267: 21432-21437] and Howard.

Eng is cited as teaching that compositions containing exendin-3 or exendin-4 can be used in methods of treating diabetes and in prevention of hyperglycemia; Howard is cited as above and Raufman is cited as teaching that GLP-1 (7-36) interacts with exendin receptors such that an exendin receptor is a GLP-1 receptor. The Examiner further states that in accordance with the present specification at page 2, full paragraph 2, "essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such treatment lowers the risk of cardiovascular disease" (page 5 of Office Action).

Thus, the Examiner is asserting that the use of exendin-3 or exendin-4 in the treatment of diabetes as taught in Eng would inherently anticipate [in this regard, Applicants note that the use of multiple references in making a rejection under 102 is normally allowed only in limited circumstances (MPEP 2131.01) where inherency is one of those circumstances] the claimed methods on the basis that essentially all diabetic patients would be patients in need of having their serum lipid levels lowered.

Applicants respectfully traverse this rejection.

Inherency regarding a missing element is a matter of certainty, not a matter of probabilities. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 28 USPQ2d 1955, 1957 (Fed. Cir.1993). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

Here, since Eng is silent as to the use of exendins to lower serum lipid levels in a patient, to establish inherency, the Examiner would have to demonstrate that every diabetic patient mentioned in Eng would necessarily be a patient in need of having his/her serum lipids lowered.

For the reasons set forth below, it is Applicants' position that the Examiner has clearly failed to support such a conclusion.

First, the paragraph of the present application that the Examiner cites to as supporting his conclusion that a patient in need of such treatment {ie lowering of serum lipid levels) is "essentially any and/or all patients, including diabetic and/or obese patients," reads as follows:

> If one concurs with the notion that atherosclerosis and associated cardiovascular diseases are related to abnormal levels of plasma lipids and lipoproteins, then lowering them represent a desirable therapeutic goal. Lowering of LDL cholesterol through treatment with statins improves on the mortality from cardiovascular diseases (Lancet 1994; 344: 1383-1389). Lowering of triglycerides through treatment with fibrates may also lower the incidence of cardiovascular diseases (Frick, MA New Engl.J.Med. 1987; 317:1237-1245). (page 2, paragraph 2 of the present application).

There is nothing in this paragraph that supports the Examiner's conclusion that Applicants have in any way defined a patient in need of the treatment recited in the present claims as being "essentially any and/or all patients, including diabetic and/or obese patients".

Second, Applicants note that although some diabetics may have elevated levels of serum lipids that require lowering, many do not. For example, the Howard reference cited by the Examiner teaches that "elevations in plasma LDL have **not** been consistently shown in individuals with diabetes" (page 216, last paragraph, emphasis added).

In addition, Applicants direct the Examiner's attention to articles by Kreisberg [Am. J. Cardiol. (1998) 82: 67U-73U] and by Wilson et al [Monogr. Atheroscler. (1985) 13:1-11], copies of which are submitted herewith. Kreisberg reports in Figure 3 on page 69U that roughly between 10-40% of type 2 diabetics have lipid abnormalities depending on the criteria measured. The Wilson article reports results from the Framingham study on levels of various lipids in diabetic and nondiabetic patients (see Table V on page 7) and clearly discloses that not all diabetic and nondiabetic patients have elevated levels of lipids. For example, Table V discloses that 19% of men and 17% of women with type 2 diabetes, and 9% and 8% of nondiabetic men and women respectively, have hypertriglyceridmemia. Thus, since only some diabetic patients are patients with elevated serum lipid levels (ie patients in need of having his/her serum lipids lowered), Eng's disclosure of the use of exendin-3 or -4 to treat diabetics does not inherently anticipate the claimed methods.

Accordingly, Applicants respectfully request withdrawal of this rejection.

REJECTION OF THE CLAIMS UNDER 35 USC 102 (b)

The Examiner rejected claims 26, 27, 29, 36, 37, 39, 40 and 42 as anticipated by Efendic (US patent 5,631,2246) in view of Howard.

Efendic is cited as teaching the treatment of obese patients with NIDDM with a GLP-1 agonist (ie GLP-1 (7-36) amide) and Howard is cited as above.

Applicants respectfully traverse this rejection.

Efendic, like Eng above, is totally silent as to the use of his GLP-1 agonist in a method for lowering serum lipid levels. Thus, as with Eng, the Examiner asserts that Efendic inherently anticipates the claimed methods on the basis that an obese patient with NIDDM would necessarily be a patient in need of having his/her serum lipids lowered.

However, based on the arguments and the Kreisberg and Wilson et al articles provided above in response to the rejection based on Eng, it is Applicants' position that the Examiner has clearly failed to support his assertion that a patient in need of the treatment recited in the present claims is "essentially any and/or all patients, including diabetic and/or obese patients".

Accordingly, since a rejection based on inherent anticipation over Efendic would require that every obese patient with NIDDM be a patient in need of having his/her serum lipids lowered, Applicants respectfully submit that Efendic cannot be held to anticipate claims 26, 27, 29, 36, 37, 39, 40 and 42 and withdrawal of this rejection is therefore respectfully requested..

REJECTION OF THE CLAIMS UNDER 35 USC 112, FIRST PARAGRAPH

A. ENABLEMENT

The Examiner rejected claims 26-29 and 36-42 as not being enabled stating: "the specification, while being enabling for a method of lowering plasma levels of triglycerides, free fatty acids, or total cholesterol, does not reasonably provide enablement for a method of lowering one or more serum lipids, of reducing the serum LDL:HDL ratio, or of reducing the serum level of lp(A) or apo(A)." (page 7 of Office Action). In particular, the Examiner stated:

"The specification envisions lowering one or more serum lipids, reducing the serum LDL:HDL ratio, and reducing the serum level of lp(A) or apo(A). The only working examples in the specification show lowering plasma levels of triglycerides, free fatty acids, or total cholesterol. The claims are directed to or encompass lowering one or more serum lipids, reducing the serum LDL:HDL ratio, and reducing the serum level of lp(A) or apo(A). However, no changes were observed in the levels of LDL and HDL cholesterol after administration of GLP-1. See Juniti-Berggren (3, cited by Applicants), page 1200, "RESULTS". This is objective evidence that the full scope of the claims is not enabled." (page 7 of Office Action).

Applicants respectfully traverse this rejection.

It is well settled that compliance with the enablement requirement of section 112, first paragraph, does not turn on whether a working example is disclosed. (see MPEP 2164.02). Thus, the absence of working examples for reducing the serum LDL:HDL ratio,

and reducing the serum level of lp(A) or apo(A) does not mean that claims to methods for reducing the levels of those lipids are nonenabled.

As stated by the Federal Circuit:
"[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be protected **must** be taken in compliance with the enabling requirement of the first paragraph of 112 **unless** there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support" Fiers v. Sugano, 984 F.2d. 1164 (Fed. Cir.1993).

Here, the Examiner has cited to Juniti-Bergren as reason to doubt that the present application enables a method of lowering one or more serum lipids, of reducing the serum LDL:HDL ratio, or of reducing the serum level of lp(A) or apo(A).

Juniti-Bergren describes a study of 12 patients in which all of them were on intensive insulin therapy the first week and from day eight, four continued with insulin and eight were given GLP-1 at meals together with regular insulin from day 8 to 12. Thus, none of the patients in the study were ever administered GLP-1 in the absence of insulin. As insulin is known to exert its own effects on lipid levels [see, for example, page 27 of the attached article by Howard et al., Metabolism, (1993) vol. 42, no 9,suppl.1, 25-35] it is Applicants' position that the coadministration of GLP-1 and insulin described in Juniti-Bergren would not teach one skilled in the art anything about the effect of GLP-1 on the serum LDL:HDL ratio, or on the serum level of lp(A) or apo(A). Accordingly, as Juniti-Bergren does not provide any evidence to doubt the objective truth of the disclosure contained in the present application, withdrawal of this rejection is respectfully requested.

B. WRITTEN DESCRIPTION

I) The Examiner rejected claims 26-29 and 36-42 as not being described in such a way as to reasonably convey to one skilled in the art that the inventors at the time the application was filed were in possession of the claimed invention. In particular, the Examiner alleged that:

"The only working examples in the specification show lowering plasma levels of triglycerides, free fatty acids, or total cholesterol. The claims are directed to or encompass lowering one or more serum lipids, reducing the serum LDL:HDL ratio, and reducing the serum level of lp(A) or apo(A). However, no changes were observed in the levels of LDL and HDL cholesterol after administration of GLP-1. See Juniti-Berggren (3, cited by

Applicants), page 1200, "RESULTS". This is objective evidence that the full scope of the claims is not described." (page 8 of Office Action).

Applicants respectfully traverse this rejection.

Here, the present application clearly describes the use of GLP-1 agonists to lower or reduce the serum LDL:HDL ratio and the serum level of lp(A) or apo(A) (see, for example, page 5, lines 7-10 and 25-28 and page 6, lines 3-8 of the application) and as discussed above, the presence of a working example is not required in an application and the coadministration of GLP-1 and insulin described in Juniti-Bergren teaches nothing about the effect of GLP-1 on the serum LDL:HDL ratio, or on the serum level of lp(A) or apo(A). Accordingly, as methods for reducing serum LDL:HDL ratio and the serum level of lp(A) or apo(A) are clearly described in the application as filed and Juniti-Bergren does not provide any evidence to doubt the objective truth of the disclosure contained in the present application, withdrawal of this rejection is respectfully requested.

II) The Examiner rejected claims 26, 27, 29, 36, 37, 39, 40 and 42 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant are that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner stated:

"The claims are directed to or encompass a GLP-1 agonist. The term "GLP-1 agonist" is a genus of compounds. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any structural limitations on the structure of the agonist." (page 8 of Office Action)

In response, Applicants respectfully submit that this rejection is rendered moot by the amendment of independent claims 26, 37 and 40 to recite that the GLP-1 agonist is GLP-1 (7-37), GLP-1 (7-36) amide, exendin-3 or exendin-4 or an analogue or derivative of any of the foregoing.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

The Examiner rejected claims 26-29 and 36-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39 and 40 of US Patent 6,268,343 or claims 19 and 20 of US Patent 6,458,924 in view of Howard and

Efendic.

The Examiner asserted that "although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is directed to or encompasses the administration of Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) for the treatment of diabetes and obesity. Essentially any and/or all patients, including diabetic and/or obese patients, including such patients with or without cardiovascular disease, are in need of such treatment because such treatment lowers the risk of cardiovascular disease in accordance with the present specification at page 2, full paragraph 2." (pages 10 and 11 of Office Action).

Applicants respectfully traverse this rejection.

These obviousness-type double patenting rejections are based on the assertion that the claimed methods of reducing serum lipid levels are obvious over the cited claims of US patents 6,268,343 and 6,458,924 because "essentially any and/or all patients, including diabetic and/or obese patients", are patients in need of having their serum lipids lowered.

However, as stated above in response to the section 102 rejections over Eng and Efendic, there is nothing in the second paragraph of page 2 of the present application that supports the Examiner's conclusion that Applicants have in any way defined a patient in need of the treatment recited in the present claims as being "essentially any and/or all patients, including diabetic and/or obese patients" and Applicants have provided evidence that not all diabetic and/or obese patients are patients with elevated serum lipids (see Applicants' reference to the Kreisberg and Wilson et al articles as set forth above in response to the rejections over Eng and Efendic).

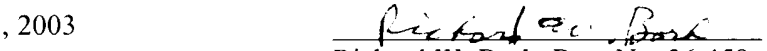
Accordingly as the cited claims of US patents 6,268,343 and 6,458,924 do not inherently disclose or suggest a method of reducing serum lipid levels in a patient, Applicants respectfully request withdrawal of these obviousness-type double patenting rejections.

In view of the above amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this response or application.

Respectfully submitted,

Date: August 25, 2003



Richard W. Bork, Reg. No. 36,459
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ –8540
(609) 987-5800

23650
PATENT TRADEMARK OFFICE